DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

94304d

Food and Drug Administration
Center for Devices and
Radiological Health
2098 Gaither Road
Rockville, MD 20850

SEP 17 2003

Via Federal Express
WARNING LETTER

Irwin Septow, O.D., Chair
Oak Lawn Institutional Review Board
4663 West 95th Street
Oak Lawn, Illinois 60453

Dear Dr. Septow:

The purpose of this Warning Letter is to inform you of objectionable conditions found during a Food and Drug Administration (FDA) inspection of your Institutional Review Board (IRB) and to request your prompt response. The inspection took place during the period of May 5 through 23, 2003, and was conducted by Ms. Lisa Hayka, an investigator from FDA's Chicago District Office. The purpose of the inspection was to determine whether your IRB procedures comply with Title 21, Code of Federal Regulations (21 CFR), Part 50 – Protection of Human Subjects, Part 56 – Institutional Review Boards, and Part 812 – Investigational Device Exemptions. These regulations apply to clinical studies of products regulated by the FDA.

Our review of the inspection report submitted by the district office revealed serious violations from pertinent regulations. You received a Form FDA 483, "Inspectional Observations," at the conclusion of the inspection that listed the deviations noted and discussed. Deviations noted include:

Failure to provide adequate initial review of investigational studies (21 CFR 56.109(a) and (b)).

IRB meeting minutes reviewed during the inspection revealed that the protocol and informed consent form for [redacted] study to evaluate the [redacted] were reviewed during an IRB meeting on [redacted]. These minutes document that the protocol was approved, but that the study investigators were not approved since a final investigator listing and investigator Curricula Vitae had not been submitted. IRB approval letters dated [redacted], however, were sent to individual investigators in this study. There is no evidence that the IRB ever reviewed information regarding the qualifications of the individual investigators or approved the final protocol version, dated [redacted].

Review of our records revealed that an inspection in June and July of 1993, when the IRB conducted business as Harold E. Davis & Associates IRB, included an extensive discussion of the IRB's practice of approving studies submitted by sponsors rather than approving clinical investigators to conduct the study as required by FDA regulations. The report from a follow-up inspection, conducted in August and September 1996, stated that the IRB was, at that time, approving individual investigators and requiring them to submit progress reports prior to conducting continuing review. Present

investigational findings reveal that the IRB has reverted to the practices noted during the 1993 inspection.

In addition, a [redacted] letter addressed to [redacted], at the consulting firm overseeing the study, stated that a revision of the informed consent form for this study was required. A dated copy of the informed consent document including signatures of IRB members was not located, however, and there is no documentation of when the revised document was approved for use.

IRB minutes also do not demonstrate that initial review of [redacted] study of [redacted] included a determination of the risk category, as required by 21 CFR Part 50, subpart D, for studies involving children.

An IRB is required to review and approve research activities and subject informed consent documentation prior to the initiation of a study. In addition, 21 CFR 56.109(e) requires an IRB to notify investigators in writing of its decisions.

Failure to provide adequate continuing review of approved studies (21 CFR 56.109(f)).

Investigational findings revealed no evidence that IRB members reviewed progress reports at least annually for the continuing review of either of the studies discussed above. Continuing review by an IRB is required by 21 CFR 56.109(f) and 21 CFR 56.115(a)(3) requires an IRB to maintain records of continuing review activities.

In addition, the IRB did not follow its own written standard operating procedures (SOPs) on continuing review for the [redacted] study. The SOPs require the IRB to initiate the reporting procedure by sending forms to the investigators at the appropriate times. If it is assumed that the study was initially approved on [redacted] requests for investigator progress reports were over six months late, as they were not sent until [redacted]

Failure to maintain adequate documentation of IRB procedures (21 CFR 56.115(a)(6)).

Review of the IRB's SOPs, which were included in the report for the recent inspection, revealed serious concerns. In general, the SOPs appear to reiterate IRB responsibilities and operations at least three times, with these iterations overlapping and often contradicting each other. The first iteration reads as if device studies, and more specifically ophthalmic device studies, are all that the IRB reviews. The later versions include information about pharmaceutical (drug and biologic) studies, but do not correctly identify the differences among study types. For example, few device studies have multiple phases and drugs are not brought to market via the 510(k) process applicable to some devices. Moreover, the third iteration of the SOPs cites the regulations in 45 CFR Part 46 and refers to the Office of Protection from Research

Risks (OPRR) in the National Institutes of Health (NIH) as the relevant office to contact. At present, however, this Office is situated in the Department of Health and Human Services (DHHS) and is called the Office for Human Research Protections (OHRP).

In addition, we note the following concerns regarding the IRB's SOPs: most of the SOP cites to 21 CFR Part 50 do not match with the regulatory text that they cite; the differences between 45 CFR Part 46 and 21 CFR Parts 50 and 56 are not adequately addressed; the discussion of exemptions, which are specific to the regulations found at 45 CFR Part 46, is interwoven with the discussion of expedited review, which is not limited to the same subset of regulations; the definition of a voting quorum does not include the need for at least one member whose primary concerns are in nonscientific areas; and the appendices, which discuss essential information, are not referred to in the body of the SOP documents.

Please revise the IRB's SOPs into a cohesive document, correcting errors and inconsistencies such as those described above. As referred to in Appendix IV of your document, information regarding IRB responsibilities is available in The FDA Information Sheets Guidance for Institutional Review Boards and Clinical Investigators, which can be found at http://www.fda.gov/oc/ohrt/irbs/default.htm. This guidance document contains a checklist of items that an IRB's SOPs should cover, as well as a listing of the differences between 45 CFR Part 46 and 21 CFR Parts 50 and 56. It is possible to write one set of SOPs incorporating each set of relevant regulations, containing the appropriate regulatory cites and also delineating differences. There is also a guide for writing SOPs for an IRB on the OHRP web site found at http://ohrp.osophs.dhhs.gov/, specifically at http://ohrp.osophs.dhhs.gov/humansubjects/guidance/irbgd702.htm.

The deviations listed above are not intended to be an all-inclusive list of the deficiencies noted and discussed. The IRB is responsible for adhering to each requirement of the law and relevant regulations.

For your information, written procedures regarding review of humanitarian use devices (HUDs) should be incorporated into your SOPs. Devices that are designated as HUDs are approved for use via the Humanitarian Device Exemption (HDE). IRB oversight is required in order for a facility to use these devices. Subpart H of 21 CFR Part 814 – Premarket Approval of Medical Devices – describes approval and use of HUDs and IRB-related requirements are set forth in 21 CFR 814.124. A copy of Subpart H is enclosed. If your IRB chooses not to review the use of HDE devices, it would be helpful to include a statement to that effect instead.

The Office of Civil Rights (OCR) in DHHS has responsibility for enforcing the regulations related to the Health Insurance Portability and Accountability Act (HIPAA). We therefore did not review the section of your SOPs related to HIPAA. If you have any questions in this regard, please reference OCR's web site which also contains contact information (http://www.hhs.gov/ocr/hipaa/).

Within fifteen (15) working days of receipt of this letter, please inform FDA of the corrective actions taken to remedy the deficiencies noted above. We realize that a complete revision of your SOPs is unlikely in this time frame. Please provide an estimate as to when we can expect receipt of a revised copy.

Please send all requested information to the Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch II (HFZ-312), 2098 Gaither Road, Rockville, Maryland 20850, Attention: Jean Toth-Allen, Ph.D. Failure to respond can lead to regulatory actions without further notice, including, as described in 21 CFR 56.120 and 56.121, withholding approval of new studies, directing that no new subjects be added to on-going studies, terminating on-going studies, notifying relevant State and Federal regulatory agencies, and initiating procedures to disqualify the IRB.

A copy of this letter has been sent to FDA's Chicago District Office, 550 W. Jackson Street, Suite 1500, Chicago, Illinois 60661. We request that a copy of your response also be sent to that office.

If you have any questions, feel free to contact Dr. Toth-Allen at (301) 594-4723, extension 141.

Sincerely yours,

Michael G. Marcarelli
for Timothy A. Ulatowski
Director
Office of Compliance
Center for Devices and Radiological Health

Enclosure

cc:

Kristine Borror, Ph.D.
Office of Human Research Protections
Department of Health and Human Services
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852